

Janowska, in further view of Waki *et al.* (*Japan Journal of Pharmacology* 79:477-483, 1999, hereinafter, "Waki"). Office Action at page 11. The Examiner relies upon Elsas, Muller and Janowska as discussed above. See Office Action at page 10. The Examiner states that these references, together, "do not teach contacting HSCs with a PDE4 inhibitor *in vivo*." Office Action at page 10. The Examiner contends that Waki supplies this missing teaching because Waki ostensibly teaches "administering 1-*n*-butyl-3-*n*-propylxanthine (XT-44), a PDE4 inhibitor, subcutaneously or orally to rats". Office Action at page 11. The Examiner thus appears to argue that, solely because XT-44 is a PDE4 inhibitor, it can be substituted for the compound of Muller. As Applicants have explained above, the combination of Elsas, Muller and Janowska does not render the amended claims obvious. One of ordinary skill in the art would not have a *reasonable* expectation of combining these references to produce the claimed methods because the effect of individual PDE4 inhibitors on the differentiation of stem or progenitor cells is too unpredictable.

The Examiner also contends that "[t]he skilled artisan would have been motivated to make such a substitution because Muller *et al.* contemplate administering [the compound] for treatment of various conditions". Office Action at page 11. As explained above, Muller does not teach or suggest administration of the compounds disclosed therein for the modulation of differentiation or proliferation of stem cells, but for the treatment of viral diseases. Moreover, nothing in the art, or in the common knowledge of a person of ordinary skill in the art, teaches or suggests that one PDE4 inhibitor is substitutable for any other PDE4 inhibitor, either generally or in the specific methods claimed in the present application. Thus, there simply is no motivation to combine Elsas, Muller, Janowska and Waki.

For the above reasons, Applicants maintain that the claims as amended are not obvious over Elsas, Muller and Janowska. Applicants respectfully request that the Examiner withdraw this rejection of the claims.

The Rejection Over Waki, Muller and Janowska

Claims 1, 2, 7-9, 11, 13, 14, 16, 25, 26, 29, 30, 32, 33 and 102 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Waki in view of Muller and Janowska. In particular, the Examiner contends that Waki teaches the treatment of mouse bone marrow with XT-44, a PDE4 inhibitor. The Examiner further contends that Janowska teaches that bone marrow comprises CD34⁺ and CD11b⁺ cells. Finally, the Examiner contends that Muller teaches the compound of formula VII. Office Action, pages 11-12.